Editorials

Prevention of Insulin-Dependent Diabetes Mellitus—Wishful Thinking, or Reality?

IN THEIR ARTICLE ELSEWHERE in this issue of the journal, Charles Verge, MB, BS, PhD, and George Eisenbarth, MD, PhD, review the natural history of insulin-dependent diabetes mellitus (IDDM) before the onset of clinical disease and also comprehensively describe the many treatments being tested worldwide to try to prevent this disease.[1] In this editorial, I will attempt to give additional emphasis to some of the topics that they have introduced.

Their figure that shows the stages in the development of type I diabetes mellitus (Figure 1) appears to depict that over time all persons who reach each respective stage will progress to subsequent stages and eventually to clinical IDDM. In fact, as noted in their text, most people with the genetic susceptibility to IDDM never progress to any of the other stages (including clinical IDDM); each of the autoantibodies associated with IDDM can occur, at least individually, in persons who do not progress to clinical IDDM; and in identical twins of patients with IDDM, immunologic and metabolic markers of IDDM occur in many more than the third who are concordant for clinical IDDM. The major point is that not all nondiabetic persons with the markers of IDDM will progress to clinical disease. The IDDM disease process may begin in some people and then go into remission. Consequently, we may never have the perfect test early in the disease process that can predict eventual clinical IDDM with complete accuracy.

Nevertheless, excellent tools for predicting the risk of clinical IDDM are available. In ICARUS (Islet Cell Antibody Register Users Study), a worldwide collaboration of more than 20 research groups,[2] data have been pooled from 456 islet cell antibody-positive first-degree relatives of IDDM patients. Of these, 108 progressed to clinical IDDM. In these persons, the combination of islet cell antibodies, insulin autoantibodies, age, and first-phase insulin response to glucose allowed a maximum risk of clinical IDDM within five years of nearly 90% to be assigned. Consecutive measurements in individual subjects over time and the addition of HLA determinations, other autoantibodies, and ultimately measures of T-cell function will likely further improve risk prediction. The IDDM disease process is dynamic and complex, probably with spontaneous remissions and relapses. With improved understanding of pathogenesis and an improved ability to accurately assess the status of the IDDM disease process, risk prediction will most assuredly improve as well.

It is easy to imagine an environmental agent or event that initiates or triggers the IDDM autoimmune disease process. But, as Drs Verge and Eisenbarth mention, it is also likely that interaction with the environment may be protective. This point is worth emphasizing. Isolating animals from environmental contact by rearing them under pathogen-free conditions increases the frequency of IDDM in both the nonobese diabetic mouse and the BB rat,[3] strongly suggesting that exposure to one or more environmental agent(s) was protective. The increasing IDDM incidence in some countries and populations cited by Drs Verge and Eisenbarth is possibly due more to the removal of or decrease in environmental protective factors than to an increase in initiating factors. If the major influence of the environment is to initiate, precipitate, or trigger the IDDM disease process, then by definition this must occur early in the disease process. In contrast, if the major influence of the environment is protective, this protection could theoretically occur any time before clinical IDDM. Of course, the two postulated roles for the environment are not mutually exclusive; some environmental factors may be initiators, and others may be protective.

Any attempt to prevent IDDM must have as a guiding principle the importance of balancing the aggressiveness of the treatment against the risk of subsequent IDDM developing. More aggressive intervention is warranted in persons with a high risk, and the obverse is true for persons at lower risk. Theoretically, if an intervention that is low in risk, inexpensive, and convenient could be discovered, perhaps we would treat everyone without even attempting to identify people at increased risk. Vaccines for certain childhood communicable diseases essentially fall into this category.

On the other end of this balance between benefit and risk, broad-spectrum immunosuppressive agents such as cyclosporine, azathioprine, and glucocorticoids have been used in newly diagnosed IDDM patients. Although some improvement in C peptide levels can be observed (as a reflection of the secretion of endogenous insulin), and the frequency and duration of remissions is improved, clinical IDDM recurs even when the drugs are continued long term.[4] Because of this limited success plus the recognized risks and toxicities associated with these drugs, it is unlikely that such broad-spectrum immunosuppressive agents will be able to achieve a positive enough benefit-to-risk ratio for their widespread use.

A precautionary comment for all trials designed to prevent IDDM is also warranted. In nonobese diabetic mice and BB rats, the development of IDDM appears to depend in large measure on the balance between effector and regulatory mechanisms.[3,5] Substrains of the nonobese diabetic mouse and BB rat that do not spontaneously develop diabetes are not missing the diabetogenic effector mechanisms. Rather, these effector mechanisms are kept under control by strong regulatory mechanisms. In both of these animal models, diabetes can be induced or accelerated by immunomodulatory therapy that decreases these regulatory mechanisms.[6,7] Effector cells capable of transferring IDDM to immune-deficient animals have even been isolated from strains of rats without a tendency for spontaneous IDDM.[8] The applicability of these observations in mice and rats to human IDDM is unknown, but, at the least, in designing clinical trials, the possibility that

some forms of immunomodulatory therapy could induce or hasten the onset of clinical IDDM must be considered. To date, the preliminary data available for the two forms of intervention therapy being tested worldwide, parenteral insulin and nicotinamide, show no evidence of possibly increasing the incidence of IDDM.

Finally, I would like to conclude by trying to guess what the results may be of the current ongoing European-Canadian Nicotinamide Diabetes Intervention Trial (ENDIT) and the Diabetes Prevention Trial, Type I (DPT-I). It is likely that both trials will be partially successful; that is, the use of either or both nicotinamide and insulin will prevent IDDM in some, but only some, high-risk persons. But this will represent a most important first step. We will have demonstrated that, at least in some people, IDDM can be prevented. Such a finding will be a tremendous stimulus to understand the mechanism underlying this success, to develop new strategies to improve on this success, and eventually to move these treatments from the research setting into clinical practice. Success in the current and future trials to prevent IDDM will usher in a new era in the treatment of diabetes. Not only will diabetologists treat patients with established diabetes, but they will also use all the combined information from genetic, immunologic, and metabolic tests to determine the risk of a person's subsequent development of IDDM. In persons at increased risk, appropriate therapy will be instituted. Those receiving such preventive therapy will be monitored immunologically and metabolically for the success or failure of their treatment, and if necessary, this treatment will be modified. Success in preventing IDDM may even pave the way for similar attacks and success in preventing other autoimmune diseases.

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